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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: USE OF VANILLOID RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PAIN

(57) Abstract: A method for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a vanilloid receptor antagonist.

WO 2004/024154 A1

## USE OF VANILLOID RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PAIN

This invention relates to a novel treatment and in particular to a method for  
5 the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional  
dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith.

Vanilloids are a class of natural and synthetic compounds that are characterised  
by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally  
equivalent group. Vanilloid Receptor (VR-1), whose function is modulated by such  
10 compounds, has been widely studied and is extensively reviewed by Szallasi and  
Blumberg (The American Society for Pharmacology and Experimental Therapeutics,  
1999, Vol. 51, No. 2.).

A wide variety of vanilloid compounds of different structures are known in the  
art, for example those disclosed in European Patent Application Numbers, EP 0 347  
15 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and  
International Patent Application, Publication Number WO 92/09285. Particularly  
notable examples of vanilloid compounds or vanilloid receptor modulators are  
capsaicin or trans 8-methyl-N-vanillyl-6-nonenamide which is isolated from the  
pepper plant, capsazepine (*Tetrahedron*, **53**, 1997, 4791) and olvanil or - N-(4-  
20 hydroxy-3-methoxybenzyl)oleamide (*J. Med. Chem.*, **36**, 1993, 2595).

US Patent Numbers, US 3,424,760 and US 3,424,761 both describe a series  
of 3-Ureidopyrrolidines that are said to exhibit analgesic, central nervous system,  
and psychopharmacological activities.

International Patent Application, Publication Number WO 01/021577  
25 discloses the preparation of a series of N-tetrahydronaphthalenyl derivatives, having  
biological activity as melanin-concentrating hormone antagonists.

International Patent Application, Publication Number WO 02/08221 discloses  
diaryl piperazine and related compounds which bind with high selectivity and high  
affinity to vanilloid receptors, especially Type I vanilloid receptors, also known as  
30 capsaicin or VR-1 receptors. The compounds are said to be useful in the treatment

of chronic and acute pain conditions, itch and urinary incontinence. International Patent Application, Publication Numbers WO 02/16317, WO 02/16318 and WO 02/16319 suggest that compounds having a high affinity for the vanilloid receptor are useful for treating stomach-duodenal ulcers.

5 International Patent Applications, Publication Numbers WO 02/072536, WO 02/090326, WO 03/022809 and WO 03/053945; and International Patent Application Number PCT/GB03/00608 also describe a variety of compounds having activity as vanilloid receptor antagonists.

10 It is now surprisingly indicated that compounds having activity as vanilloid receptor antagonists have activity in the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith.

Accordingly, the invention provides a method for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's  
15 metaplasia, dysphagia and pain associated therewith, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a vanilloid receptor antagonist.

Suitably, the invention provides a method for the treatment and/or prophylaxis of pelvic pain.

20 Suitably, the invention provides a method for the treatment and/or prophylaxis of renal colic or pain associated therewith.

Suitably, the invention provides a method for the treatment and/or prophylaxis of biliary colic or pain associated therewith.

25 Suitably, the invention provides a method for the treatment and/or prophylaxis of functional dyspepsia or pain associated therewith, such as, heartburn.

Suitably, the invention provides a method for the treatment and/or prophylaxis of Barrett's metaplasia or pain associated therewith.

Suitably, the invention provides a method for the treatment and/or prophylaxis of dysphagia or pain associated therewith.

Suitably, the vanilloid receptor antagonist is an antagonist of the vanilloid receptor-1.

Suitable vanilloid receptor antagonists for use in accordance with the present invention include those disclosed in European Patent numbers EP 0 347 000 and EP 0 401 903; UK Patent Application Number GB 2226313; International Patent Applications, Publication Numbers WO 92/09285, WO 01/021577, WO 02/08221, WO 02/16317, WO 02/16318, WO 02/16319, WO 02/072536, WO 02/090326, WO 03/022809 and WO 03/053945; International Patent Application Number PCT/GB03/00608; and US Patent Numbers, US 3,424,760 and US 3,424,761.

Preferred vanilloid receptor antagonists for use in accordance with the present invention include those disclosed in International Patent Applications, Publication Numbers WO 02/072536, WO 02/090326, WO 03/022809 and WO 03/053945; and International Patent Application Number PCT/GB03/00608.

A particularly preferred vanilloid receptor antagonist for use in accordance with the present invention is *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea (hereafter referred to as "Compound A"), or a pharmaceutically acceptable derivative thereof. Compound A is disclosed at Example 1 of International Patent Application, Publication Number WO 03/022809.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Certain vanilloid receptor antagonists may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. Where a vanilloid receptor antagonist contains a chiral carbon, and hence exists in one or more stereoisomeric forms or where one or more geometric isomers exist, it will be appreciated that the method of the present invention encompasses all of the said forms of the vanilloid receptor

antagonists whether as individual isomers or as mixtures of isomers, including racemates.

When used herein the term 'vanilloid receptor antagonist' relates to an antagonist, such as a small molecular weight antagonist, of the vanilloid receptor. It  
5 will be appreciated that the term also embraces suitable pharmaceutically acceptable derivatives thereof.

Vanilloid receptor antagonist activity may be assessed by use of the methodologies disclosed in the above-mentioned patent applications, such as, WO 02/08221, WO 02/16317 and WO 02/090326.

10 Suitable pharmaceutically acceptable derivatives of a vanilloid receptor antagonist are, for example, salts and solvates.

Suitable pharmaceutically acceptable derivatives of any particular vanilloid receptor antagonist include those disclosed in the above-mentioned publications.

Suitable pharmaceutically acceptable salts include salts derived from  
15 appropriate acids, such as acid addition salts, or bases.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine,  
20 hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

25 Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulfate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulfonate,  $\alpha$ -keto glutarate and  $\alpha$ -glycerophosphate, especially the maleate salt.

The vanilloid receptor antagonists referred to herein are conveniently prepared according to the methods disclosed in the above mentioned patent publications in which they are disclosed.

5 The salts and/or solvates of the vanilloid receptor antagonists referred to herein may be prepared and isolated according to conventional procedures for example those disclosed in the above mentioned patent publications.

The present invention also provides a vanilloid receptor antagonist or a pharmaceutically acceptable derivative thereof, for use in the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's  
10 metaplasia, dysphagia and pain associated therewith.

The present invention also provides a vanilloid receptor antagonist or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated  
15 therewith.

In the above-mentioned method the vanilloid receptor antagonist, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

20 In the treatment of the invention, the vanilloid receptor antagonist mentioned herein is formulated and administered in accordance with the methods disclosed in the above mentioned patent applications and patents.

Accordingly, the present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated  
25 therewith, which composition comprises a vanilloid antagonist, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other  
5 routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may  
10 comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

15 Suitable dosages of the vanilloid receptor antagonist include the known doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the  
20 above mentioned publications or doses which can be determined by standard procedures.

The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities  
25 of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water  
30 or other suitable vehicle before use. Such liquid preparations may contain

conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible  
5 oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing  
10 the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the  
15 vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before  
20 suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

25 Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.),



Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

No adverse toxicological effects are expected for the compositions or methods of the invention in the above mentioned dosage ranges.

### Claims

- 5 1. A method for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a vanilloid receptor antagonist.
- 10 2. A method according to claim 1, for the treatment and/or prophylaxis of renal colic or pain associated therewith.
- 15 3. A method according to claim 1, for the treatment and/or prophylaxis of biliary colic or pain associated therewith.
4. A method according to claim 1, for the treatment and/or prophylaxis of functional dyspepsia or pain associated therewith, such as, heartburn.
- 20 5. A method according to claim 1, for the treatment and/or prophylaxis of Barrett's metaplasia or pain associated therewith.
6. A method according to claim 1, for the treatment and/or prophylaxis of dysphagia or pain associated therewith.
- 25 7. A method according to claim 1, wherein the vanilloid receptor antagonist is an antagonist of the vanilloid receptor-1.
8. A method according to claim 7, wherein the vanilloid receptor-1 antagonist is *N*-(2-Bromophenyl)-*N'*-[*((R)*-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea.
- 30

9. A pharmaceutical composition for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith, which composition comprises a vanilloid antagonist, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.
10. A vanilloid receptor antagonist or a pharmaceutically acceptable derivative thereof, for use in the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith.
11. A vanilloid receptor antagonist or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10261

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4439 A61K45/00 A61P1/00 A61P13/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, EMBASE, MEDLINE, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 08221 A (BAKTHAVATCHALAM RAJAGOPAL ; DESIMONE ROBERT W (US); NEUROGEN CORP ( ) 31 January 2002 (2002-01-31) cited in the application page 1 -page 37 in particular p. 32, claim 192 ---	1,7-11
X	WO 02 16317 A (KIM HEE DOO ; LEE JEE WOO (KR); PARK YOUNG HO (KR); SUH YOUNG GER ( ) 28 February 2002 (2002-02-28) cited in the application page 1 -page 7 page 24, line 8 - line 13 in particular p. 4 page 93, line 8 page 95, line 11 -page 96, line 2 claims --- -/--	1,4,7, 9-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

29 January 2004

Date of mailing of the international search report

12/02/2004

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10261

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 63986 A (DETTMAR PETER WILLIAM ;JOLLIFFE IAN GORDON (GB); GARDINER FIONA (G) 16 December 1999 (1999-12-16) page 5, line 13 -page 6, line 2 ---	1,4-7, 9-11
X	BORTOLOTTI M ET AL: "The treatment of functional dyspepsia with red pepper" ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, vol. 16, no. 6, June 2002 (2002-06), pages 1075-1082, XP001157342 ISSN: 0269-2813 the whole document ---	1,4-7, 9-11
X	LAZZERI M ET AL: "Intravesical capsaicin for treatment of severe bladder pain: A randomized placebo controlled study" JOURNAL OF UROLOGY, vol. 156, no. 3, 1996, pages 947-952, XP009024463 ISSN: 0022-5347 the whole document ---	1,7,9-11
P,X	WO 03 022809 A (RAMI HARSHAD KANTILAL ;WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB) 20 March 2003 (2003-03-20) cited in the application page 2 -page 10 page 33 page 15, line 15 - line 32 example 1 ---	1-11
P,X	WO 03 053945 A (RAMI HARSHAD KANTILAL ;THOMPSON MERVYN (GB); SMITHKLINE BEECHAM PL) 3 July 2003 (2003-07-03) cited in the application page 2 -page 5 page 10, line 17 - line 33 ---	1-11
P,X	WO 03 068749 A (MITCHELL DARREN JASON ;RAMI HARSHAD KANTILAL (GB); GLAXO GROUP LTD) 21 August 2003 (2003-08-21) page 2, line 26 -page 21 page 33, line 5 - line 33 ---	1-11
P,X	WO 02 072536 A (WYMAN PAUL ADRIAN ;GLAXOSMITHKLINE (GB); THOMPSON MERVYN (GB); SMI) 19 September 2002 (2002-09-19) cited in the application page 1 -page 3 page 4, line 36 -page 5, line 8 ---	1-11
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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10261

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 02 090326 A (RAMI HARSHAD KANTILAL ;WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB) 14 November 2002 (2002-11-14) cited in the application page 1 -page 3 page 5, line 24 - line 36 -----</p>	1-11

Continuation of Box I.2

The subject-matter of present claims 1-7 and 9-11 is defined by means of the functional feature 'vanilloid receptor antagonist'.

The functional feature relates to a large number of possible compounds, and it is not clear which compounds, structurally defined, are encompassed in the definition (Art. 6 PCT).

Because of the character of the functional feature, it cannot be guaranteed that the performed search is complete.

It cannot be excluded that compounds fulfilling the requirements of the functional feature have not been identified as doing so in the prior art.

If such compounds have not been identified in the application either, they have not been covered by the search.

The search has been carried out, based on the functional feature per se as well as on the compounds which are disclosed in the documents to which reference is made in the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/10261

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10261

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0208221	A	31-01-2002	AU 8066701 A	05-02-2002
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			CA 2415606 A1	31-01-2002
			CN 1443170 T	17-09-2003
			EP 1301484 A2	16-04-2003
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